Formal Allylic C(sp(3))-H Bond Activation of Alkenes Triggered by a Sodium Amide

Formal Allylic C(sp^3)–H Bond Activation of Alkenes Triggered by a Sodium Amide

Wei Bao,[+] Hanno Kossen[+] and Uwe Schneider*

The University of Edinburgh, EaStCHEM School of Chemistry, The King's Buildings, David Brewster Road, EH9 3FJ Edinburgh, UK

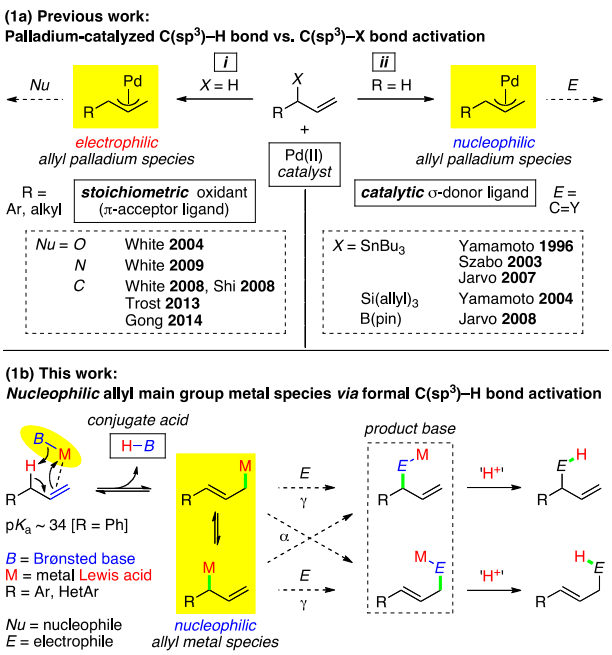
Supporting Information Placeholder

ABSTRACT: The catalytic use of a sodium amide has been exploited for formal allylic C(sp^3)–H bond activation of alkenes under mild conditions. Subsequent C–C bond formations with imines have proceeded in high yields with complete regio- and excellent geometric selectivities. Aromatic cyano, chloro, and bromo functionalities have proved to be tolerated by the transition metal-free catalyst. Complex amines bearing a C=C double bond and distinct heteroaromatic units have been prepared in a single step. The critical importance of sodium vs. other s-, p-, d-, and f-block metals as well as metal-free systems has been revealed. In addition, two catalytically active sodium-based intermediates were detected by NMR and HRMS analyses.

The past decades have witnessed tremendous advances in organic chemistry through the development of catalytic C–H bond activation.[1] Typically, transition metal catalysts have been used to activate both C(sp^2)–H[2] and C(sp^3)–H[3] bonds. In the context of *allylic* C(sp^3)–H bond activation of alkenes, White *et al.* reported in 2004 a ligated palladium(II) acetate catalyst to generate an *electrophilic* allyl–Pd intermediate, which underwent C–O bond formation with a suitable nucleophile *Nu* (Scheme 1a–*i*);[4] this transformation relies on a stoichiometric amount of benzoquinone as an oxidant serving also as a π-acceptor ligand. To date, this *oxidative* C–H bond activation has been exploited for C–N[5] and C–C[6] bond formations, respectively, including asymmetric catalysis (Scheme 1a–*i*). Palladium-free methods include the use of first-row transition metal catalysts in the presence of a stoichiometric oxidant.[7]

Generally, electrophilic allyl–Pd species may undergo *reductive umpolung* to generate a nucleophilic allyl–M intermediate,[8] but this strategy is precluded for oxidative C–H bond activation. Typically, only metalated or metalloid allyl substrates were shown to serve as suitable precursors to *nucleophilic* allyl–Pd species (Scheme 1a–*ii*). In 1996, Yamamoto *et al.* have activated an allyl stannane to form the corresponding Pd intermediate for nucleophilic addition to a suitable electrophile *E*.[9] This methodology relies on the use of an anionic and/or electron-rich σ-donor ligand.[10] Recently, this concept has been extended to the use of silicon[11] and boron[12] pro-nucleophiles, respectively (Scheme 1a–*ii*). In the context of using imine electrophiles,[13] alternative Pd-free catalysis has been exploited as well.[14] To the best of our knowledge, however, the generation of a *nucleophilic allyl–M* species through *catalytic C–H bond activation* has not been achieved yet.

Scheme 1. Background and concept.



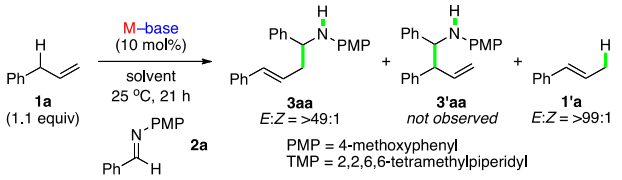
In our program exploiting non-precious metal–base catalysts for formal C–H bond activation, we have become interested in the activation of challenging pro-nucleophiles, such as terminal alkenes, in view of subsequent bond formations (Scheme 1b). Judging from the reported pK_a value of 34 for the allylic hydrogen (R = Ph),[15] we anticipated that a metal *π-Lewis acid* may be

required to acidify the hydrogen for deprotonation by an amide *Brønsted base* ($B = NR_2$). In this scenario, a *nucleophilic* allyl–M species would be generated directly *via* formal C–H bond activation (Scheme 1b). This intermediate may undergo C–C bond formation with a suitable electrophile *E* (e.g. imine) to form another metal amide (product base), which may account for turnover of the catalytically active allyl–M species. A selective transformation of this type was expected to be challenging because the allyl intermediate may undergo metallotropic rearrangement *and* γ- or α-selective C–C bond formation thus potentially leading to product mixtures (Scheme 1b). We report here the catalytic use of a sodium amide for formal C(sp^3)–H bond activation of alkenes in view of C–C bond formations with imines.

In initial experiments, allyl benzene (**1a**) and benzaldehyde-derived PMP-protected imine **2a** were used as substrates in the presence of a metal amide (10 mol%) at 25 °C (Table 1). The use of commercially available lithium amides in dioxane failed to mediate a C–C bond formation (entries 1–3). When the reaction was carried out in a more Lewis basic solvent, THF, linear adduct **3aa** was obtained in up to 56% yield (*E*:*Z* = >49:1; entry 1); while regioisomer **3'aa** was not detected, internal alkene **1'a** was observed as a side-product in up to 13% yield (*E*:*Z* = >99:1; entry 1). When sodium hexamethyldisilazide was used in dioxane, the intended product **3aa** was formed in 98% yield (*E*:*Z* = 99:1), alongside a trace of **1'a** (entry 4); the yield of **3aa** significantly decreased in THF (entry 4). A screening has revealed that various other etheral solvents and *N*-phenyl-protected imines were compatible with the sodium amide catalyst (see SI). Interestingly, when the stronger potassium base was used the yield of product **3aa** dropped to 23% (entry 5). We also examined a range of other commercially available or easily accessible metal hexamethyldisilazides (entries 6–9). Alkaline earth and p-block metal amides have proved to be unreactive in dioxane or THF (Mg, Ca, Sr, Sn; entry 6). Furthermore, d- and f-block metal amides failed to give **3aa** (Cu, Ag, Zn, Ce, Eu, Gd; entries 7–9). Similarly, the use of alkali metal hydrides –as stronger bases– has proved to be ineffective (entry 10). On the other hand, methyl lithium was shown to trigger a C–C bond formation; product **3aa** and side-product **1'a** were formed in up to 59% and 20% yields, respectively (entry 11). It is noted that the loading of the most effective mediator, $NaN(SiMe_3)_2$, was decreased to 5 mol% without loss of activity (entry 12). In this context, the unique ability of sodium and $NaN(SiMe_3)_2$ was confirmed through further catalysis control experiments and inductively coupled plasma (ICP) trace element/metal analysis (see SI). In addition, a robustness screening has revealed that several important functionalities were tolerated (see SI). Finally, the critical importance of a metal ion *per se* was demonstrated by using various strong organobases; product **3aa** was *not* obtained under *metal-free* conditions (see SI).

Our study has revealed several remarkable features of this main group metal Brønsted *base* 'catalysis': (1) the connectivity of the alkene and the electronic demand of the imine are clearly distinct from the imino-ene reaction,[16] which relies on transition metal Lewis *acid* catalysis; (2) the *catalytic* activation of the alkene with a Na amide stands in sharp contrast to the *super-stoichiometric* use of a Li amide for Pd-catalyzed cross-coupling, which also proceeded with opposite regioselectivity;[17] (3) while Na is among the most abundant and cheap metals,[18] only sporadic examples for the catalytic use of a Na amide have been reported in C–C bond formation;[19] (4) the obtained 'negative' data (Table 1, entries 6–9) contrast the Brønsted base catalysis with s-, d-, and f-block metal amides in organic synthesis,[20] and stress the challenging character of this Na amide-triggered alkene–imine cross-coupling. The fact that Na has proved to be superior to other metals, including Li and K, may be ascribed to favorable values[21] of electronegativity, formal charge, and ionic radius, all of which should influence both metal Lewis acidity and amide Brønsted basicity.[22]

Table 1. Metal–base screening.[a]



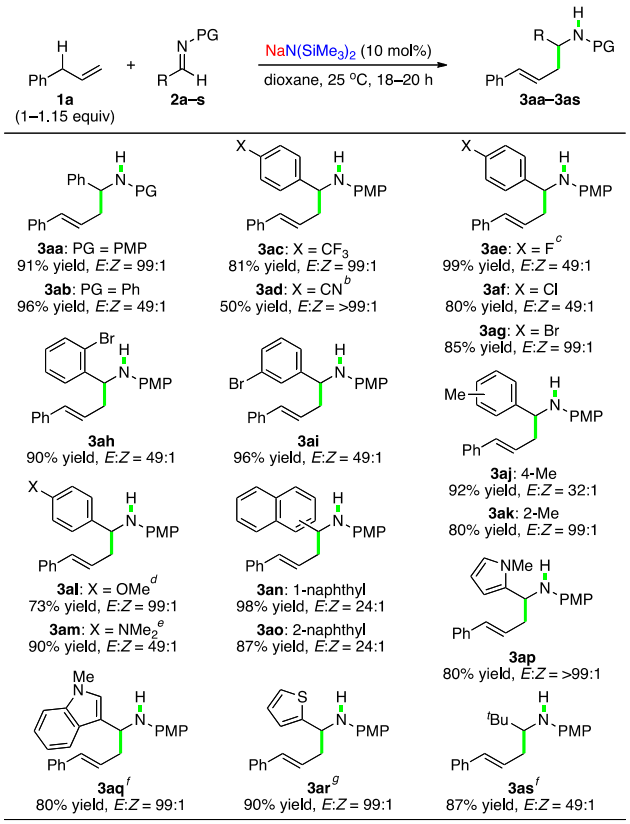
entry	M–base	in dioxane: yield[a] [%] **3aa** / **1'a**	in THF: yield[a] [%] **3aa** / **1'a**
1	LiN^iPr_2	NR	56 / 13
2	LiTMP	NR	32 / 2
3	$LiN(SiMe_3)_2$	NR	42 / 4
4[b,c]	$NaN(SiMe_3)_2$	98 / 5	40 / 0
5	$KN(SiMe_3)_2$	23 / 44	0 / 37
6	$M[N(SiMe_3)_2]_2$ M = Mg, Ca, Sr, Sn	NR	NR
7	$MN(SiMe_3)_2$ M = Cu, Ag	NR	–
8	$Zn[N(SiMe_3)_2]_2$	NR	–
9	$M[N(SiMe_3)_2]_3$ M = Ce, Eu, Gd	NR	–
10	MH M = Li, Na, K [50 mol%]	NR	NR
11[d]	LiMe	14 / 2	59 / 20
12[e,f]	$NaN(SiMe_3)_2$ [5 mol%]	99 / 5	–

[a] Yields are ^{1}H NMR yields determined with an aliquot vs. Bn_2O as internal standard. [b] The use of other etheral solvents gave **3aa** in 14–87% yields (see SI). [c] A screening of *N*-protecting groups revealed that *N*-Ph-protected imines are reactive as well (see SI). [d] Nucleophilic methyl addition to the C=N double bond of **2a** was not detected. [e] A robustness screening confirmed that various important functionalities were tolerated by the sodium amide catalyst (see SI). [f] Metal-free strong organobases have proved to be ineffective (see SI).

Next, the imine scope was examined for the Na amide-triggered C–C bond formation using alkene **1a** (Scheme 2). Various electron-poor aromatic imines were successfully converted to cross-coupled products in 50–99% yields (*E*:*Z* = ≥49:1; **3ab–ai**). Aromatic rings with *o*-, *m*-, and *p*-substitution and sensitive functional groups –such as cyano, chloro, and bromo– were tolerated by the transition metal-free catalyst. Likewise, the use of electron-rich aromatic imines gave the corresponding products in 73–98% yields (*E*:*Z* = ≥24:1; **3aj–ao**). Additionally, a variety of heterocyclic imines were shown to be excellent substrates (80–90% yields, *E*:*Z* = ≥99:1; **3ap–**

ar). Moreover, a tertiary aliphatic imine –derived from pivaldehyde– reacted smoothly to give product **3as** in 87% yield (*E*:*Z* = 49:1).

Scheme 2. Scope of imines.

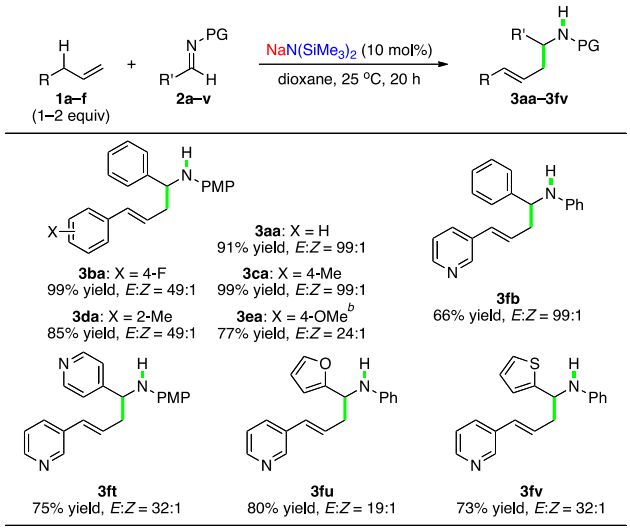


[a] All yields are isolated yields after preparative thin-layer chromatography (PTLC). [b] Use of 3 equiv of **1a**. [c] Reaction conducted at 40 °C. [d] Use of 1.8 equiv of **1a** (successive addition). [e] Use of 2.5 equiv of **1a** (successive addition). [f] Use of 2 equiv of **1a** (successive addition). [g] Reaction conducted with 1.5 equiv of **1a** at 60 °C for 72 h.

In addition, the scope of alkenes was examined (Scheme 3). Variously substituted allyl benzenes **1b–e** were shown to react smoothly to give the corresponding products in 77–99% yields (*E*:*Z* = ≥24:1; **3ba–ea**). Furthermore, 3-allyl pyridine (**1f**) has proved to be an excellent pro-nucleophile to give, with a variety of imines, cross-coupled products in 66–80% yields (*E*:*Z* = ≥19:1). Complex amines bearing a C=C double bond and two electron-poor *N*-heterocycles (**3ft**), or both electron-poor and electron-rich heteroaromatic units (**3fu**, **3fv**), were formed in a single step.

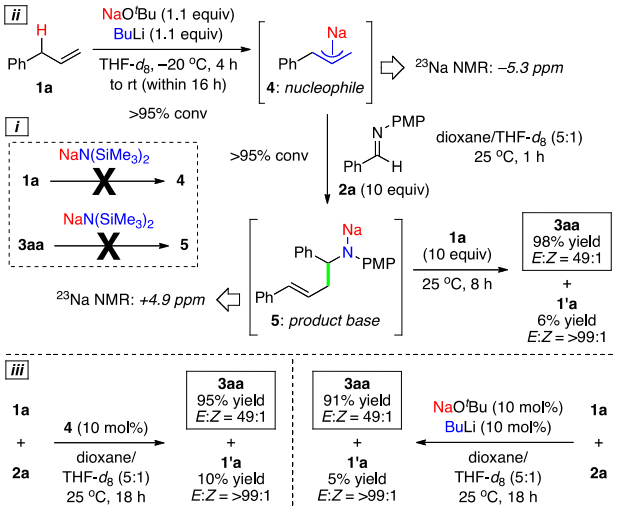
Finally, we investigated the reaction mechanism (Scheme 4). Allyl–Na species **4** was not detectable in the reaction between alkene **1a** and NaN(SiMe$_3$)$_2$ under various conditions (Scheme 4–*i*); instead, a mixture of isomers **1a** and **1'a** was observed, which may be ascribed to the high reactivity of **4** in the presence of a proton source [HN(SiMe$_3$)$_2$]. However, when **1a** was reacted with NaO^{t}Bu/BuLi (1.1 equiv) in THF-d_8 at –20 °C, a single resonance at –5.3 ppm was detected in ^{23}Na NMR spectroscopy, which is consistent with a Na–C species (Scheme 4–*ii*; see SI).[23] Together with ^{1}H/^{13}C NMR and HRMS data, this intermediate was assigned to be the η^3-coordinated (*E*)-phenylallyl–Na *nucleophile* **4** (see SI). Species **4** underwent C–C bond formation with imine **2a** (10 equiv) to generate the Na–N *product base* **5** as detected in ^{23}Na (+4.9 ppm) and ^{1}H/^{13}C NMR spectroscopy (Scheme 4–*ii*; see SI).[24] Species **5** proved to be catalytically active; when **1a** (10 equiv) was added to the mixture, product **3aa** was formed in 98% yield (*E*:*Z* = 49:1) based on **2a** (Scheme 4–*ii*). Likewise, species **4** and NaO^{t}Bu/BuLi were shown to catalyze the reaction between **1a** and **2a** to give **3aa** in 95% and 91% yields, respectively (*E*:*Z* = 49:1; Scheme 4–*iii*).[25] These results are consistent with the data obtained for the catalytic use of NaN(SiMe$_3$)$_2$ (cf. Table 1, entry 4), and suggest that species **4** and **5** are critical intermediates in the developed sodium amide catalysis.

Scheme 3. Scope of alkenes.



[a] All yields are isolated yields after preparative thin-layer chromatography (PTLC). [b] Reaction conducted at 40 °C.

Scheme 4. Mechanistic experiments.



In conclusion, we have developed a sodium amide-triggered formal C(sp^3)–H bond activation of alkenes under mild conditions, which was exploited for atom-economic C–C bond formations with imines proceeding in high yields with complete regio- and excellent geometric

selectivities. Aromatic cyano, chloro, and bromo functionalities have proved to be tolerated by the transition metal-free catalyst. The critical importance of sodium vs. other s-, p-, d-, and f-block metals as well as metal-free systems has been demonstrated. Two novel catalytically active sodium-based intermediates were detected, which sheds light on the reaction mechanism. This methodology is a rare example for the catalytic use of a sodium amide in C–C bond formation,[19] and should impact the fields of organic synthesis, main group metal chemistry, and earth-abundant[18] metal catalysis.

ASSOCIATED CONTENT

Experimental details and characterization data.

AUTHOR INFORMATION

Corresponding Author

*uwe.schneider@ed.ac.uk

Notes

[+] These authors contributed equally to this work.

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

Eli Lilly, the School of Chemistry, the University of Edinburgh, the Royal Society, and the EU (PCIG10–GA–2011–304218) are greatly acknowledged for financial support.

REFERENCES

(1) *C–H Bond Activation and Catalytic Functionalization I*; Dixneuf, P. H.; Doucet, H., Eds.; *Topics in Organometallic Chemistry*; Springer International Publishing: Switzerland, 2015; Vol. 55.

(2) Selected examples: (a) Pd: Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Fe: Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (c) Co: Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279.

(3) Selected examples: (a) Review on catalysis with precious transition metals: Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Fe: Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (c) Cu: Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851.

(4) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (d) Ammann, S. E.; Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 10834. (e) Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem., Int. Ed.* **2016**, *55*, 9571.

(5) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701.

(6) (a) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901. (b) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (c) Trost, B. M.; Thaisrivongs, D. A.; Donckele, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1523. (d) Wang, P.-S.; Lin, H.-C.; Zhai, Y.-J.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 12218. (e) Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipow, M.; Masters, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 2776.

(7) Formally *electrophilic* allyl–M species: Cu(I): (a) Andras, M. B.; Zhou, Z. *J. Am. Chem. Soc.* **2002**, *124*, 8806. (b) Zhou, Z.; Andras, M. B. *Tetrahedron Lett.* **2012**, *53*, 4518. (c) Fe: Sekine, M.; Ilies, L.; Nakamura, E. *Org. Lett.* **2013**, *15*, 714. (d) Cu(II): Huang, X.-F.; Salmon, M.; Huang, Z.-Z. *Chem. – Eur. J.* **2014**, *20*, 6618.

(8) Lead reference for the *stoichiometric umpolung* of *electrophilic* allyl–Pd to *nucleophilic* allyl–M species: Tamaru, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley–Interscience: New York, 2002; Vol. 2, pp 1917.

(9) (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (c) Solin, N.; Kjellgren, J.; Szabo, K. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3656. (d) Fernandez, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133. (e) Solin, N.; Kjellgren, J.; Szabo, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026. (f) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863.

(10) Lead references: (a) Concept: Szabo, K. J. *Chem – Eur. J.* **2004**, *10*, 5268. (b) Yamamoto, Y.; Nakamura, I. In *Palladium in Organic Synthesis*; Tsuji, J., Ed.; *Topics in Organometallic Chemistry 14*; Springer Verlag: New York, 2005; Vol. 14, pp 211.

(11) Fernandez, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735.

(12) (a) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743. (b) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2009**, *65*, 3197.

(13) Review: Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(14) *Nucleophilic* allyl–M species: (a) C–Sn bond activation; Zr: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896. C–Si bond activation: (b) Cu: Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615. (c) Huber, J. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 14552. (d) Ag: Naodovic, M.; Wadamoto, M.; Yamamoto, H. *Eur. J. Org. Chem.* **2009**, 5129. C–B bond activation: (e) Cu: Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (f) Cu: Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332. (g) Rh: Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam., H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309.

(15) Bowden, K.; Cook, R. S. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1407.

(16) A *silylated* alkene was required to access the same product constitution: Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, III, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67.

(17) Hussain, N.; Frensch, G.; Zhang, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3693.

(18) Abundance in the Earth's crust – Na (23.000 ppm) vs. Pd (0.0063 ppm): https://www.webelements.com/periodicity/abundance_crust/

(19) (a) Na amide Lewis base catalysis: Tabassum, S; Sereda, O.; Reddy, P. V. G.; Wilhelm, R. *Org. Biomol. Chem.* **2009**, *7*, 4009. (b) Na amide co-catalyst in asymmetric Nd catalysis: Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860. (c) see ref 20a (single example).

(20) (a) K: Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 4336. (b) Ca: Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042. (c) Sr: Kobayashi, S.; Yamaguchi, M.; Agostinho, M.; Schneider, U. *Chem. Lett.* **2009**, *38*, 296. (d) Cu: Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049. (e) Ag: Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262. (f) Gd: Nagae, H.; Shibata, Y.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2015**, *137*, 640.

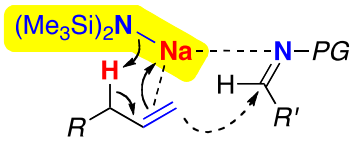
(21) https://www.webelements.com/sodium/

(22) Metal as a key to structure and reactivity of amides: (a) Mulvey, R. E.; Robertson, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1470. (b) Penafiel, J.; Maron, L.; Harder, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 201.

(23) The direct conversion **1a → 4** failed when other Na bases ($NaNH_2$, NaH, NaBu) were used under various conditions.

(24) The direct conversion **3aa → 5** failed (Scheme 4–*i*).

(25) In contrast, when the Li analogue of **4** was used (10 mol%), product **3aa** was obtained in only 12% yield (*E*:*Z* = >99:1; see SI).



pK_a ~ **34** [R = Ph]

R = Ar, 3-py
R′ = Ar, HetAr, ^{t}Bu; *PG* = PMP, Ph

*generation of **nucleophilic allyl–Na** species via formal catalytic **C(sp^3)–H** bond activation*

– transition metal-free method
– 27 examples
– complete regioselectivity
– *E*:*Z* = 19:1 ~ >99:1
– detection of novel Na intermediates